

# Assessing the see-and-treat approach for the management of high-grade squamous intraepithelial cervical lesions

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## Abstract

**Objectives:** To assess local histological outcomes in patients with HSIL cytology results on cervical smears, in both the see-and-treat and three-step approach.

**Study Design:** A retrospective analysis of patients with HSIL on cervical cytology was performed, obtaining an 83 patient cohort. The histological result following the primary investigation (colposcopic-directed biopsy or excisional procedure) was noted for each patient together with their demographic variables and HPV status.

**Results:** Of 83 patients with HSIL cytology on cervical smear, 43 underwent LLETZ as a primary procedure, while 40 patients underwent a colposcopic-directed biopsy. There was no statistically significant difference in terms of demographics and HPV status between the two groups. In those patients who had LLETZ as a primary procedure, 29 had CIN2+ on histology. On the other hand, following colposcopic-directed biopsies, 17 resulted in CIN2+ on histology.

**Conclusion:** The conventional approach within our local setting potentially has inferior sensitivity in picking up CIN2+ lesions when compared to the see-and-treat approach. On the other hand, primary excisional procedures were associated with an overtreatment rate of at least 20.9%, subjecting patients to unnecessary risks. Local improvement of colposcopic skill will aid to reduce this overtreatment rate and missed lesions at biopsy.

## Keywords

Colposcopy, Cervical intraepithelial neoplasia, Squamous Intraepithelial Lesions of the Cervix, Overtreatment, Diagnostic Errors

## Introduction

Cervical carcinoma is the fourth most common malignancy in women worldwide, with an estimated 4.68 per 100,000 being affected locally per year while 9.8 per 100,000 are affected in the UK per year.<sup>1</sup> Cervical cancer is in the large majority of cases preceded by Human Papilloma Virus (HPV) infection and pre-malignant changes, with HPV 16 and 18 responsible for about 70% of all cases. HPV persistence results in the integration of viral genetic material into the cellular genome, inactivating tumour suppressor function leading to genetic instability and precancerous changes.<sup>2</sup> Cervical screening and HPV typing through a

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Papanicolaou smear or liquid based cytology form the basis of cervical cancer screening programmes worldwide.

High-grade squamous intraepithelial lesion (HSIL) on cervical cytology is one of the categories of the Bethesda classification system used in cervical screening programmes. HSIL cytology results identify women at substantial risk of cervical intraepithelial neoplasia (CIN).<sup>3</sup> Women with HSIL carry a 7% five-year risk of cervical cancer regardless of HPV status.<sup>4</sup>

In most screening algorithms, abnormal cervical cytology is followed up by colposcopically-directed cervical biopsies. If CIN2+ is detected on colposcopic biopsies, the cervix may be treated by excising the transformation zone by using various methods, such as a large loop excision of the transformation zone (LLETZ). This is referred to as the conventional three-step approach.<sup>5</sup>

Bigrigg<sup>6</sup> initially pioneered the see-and-treat protocol for women with abnormal smear results. This approach involves assessing the cervix macroscopically at colposcopy and directly performing a LLETZ procedure should abnormal epithelial changes be confirmed. Therefore in this approach simultaneous histologic diagnosis and treatment is carried out.<sup>2</sup> Some 60% of women with HSIL on cervical cytology are found to have CIN2+ on histology. Thus the American Society for Colposcopy and Cervical Pathology (ASCCP) recommends immediate excision of the transformation zone for non-pregnant females over the age of 25, especially if colposcopic examination is inadequate. However, primary colposcopy including full assessment of the transformation zone is also an acceptable approach.<sup>3</sup>

Both approaches have their drawbacks. Overtreatment is a potential drawback of the 'see-and-treat' approach, whereby patients might undergo excisional procedures only to have normal or low-grade results on histopathological assessment. On the other hand, high-grade CIN may be under evaluated in colposcopic-directed biopsies, partly due to the subjectivity involved in the selection of the site for biopsies.<sup>7</sup>

This study aims to assess local histological outcomes in patients with HSIL cytology results on

cervical smears, in both the see-and-treat and three-step approach.

## Methodology

This study is a retrospective analysis of an 83 patient cohort gathered over two years (2015-2017). Patients with HSIL on cervical cytology were identified through Mater Dei Hospital's histopathological records after the appropriate data protection approval was acquired.

Demographic variables and HPV status, including serotypes present, were noted for each patient with an HSIL cytological result. The histological result following the primary investigation in their management plan (colposcopic-directed biopsy or excisional procedure) were evaluated.

## Results

Of 83 patients with HSIL cytology on cervical smear, 51.8% ( $n=43$ ) underwent LLETZ as a primary procedure, while 48.2% ( $n=40$ ) patients underwent a colposcopic-directed biopsy. Of the latter, 14 patients required a LLETZ procedure after their first colposcopic-directed biopsy, while 4 patients underwent a repeat colposcopy, two of which ultimately required a LLETZ procedure. The remaining 22 patients were followed up with cervical cytology (Figure 1). The transformation zone was present in 98.8% of cervical biopsies taken.

There were no statistically significant differences in mean patient age and HPV positivity on statistical analysis of the two main treatment arms with a non-paired student t-test. The mean age of the LLETZ group was 34.4 years, while the mean age of the colposcopic-directed biopsy group was 35.1 ( $p=0.5917$ ). The HPV risk profiles were also very similar between the two groups (Table 1).

In those patients who had LLETZ as a primary procedure, 67% ( $n=29$ ) had CIN2+ on histology. On the other hand, following colposcopic-directed biopsies, 42.5% ( $n=17$ ) resulted in CIN2+ on histology (Figure 2 and Table 2). Figure 3 shows a more detailed breakdown of histological results according to the management approach taken.

Figure 1: Management pathway for HSIL patients included in the study

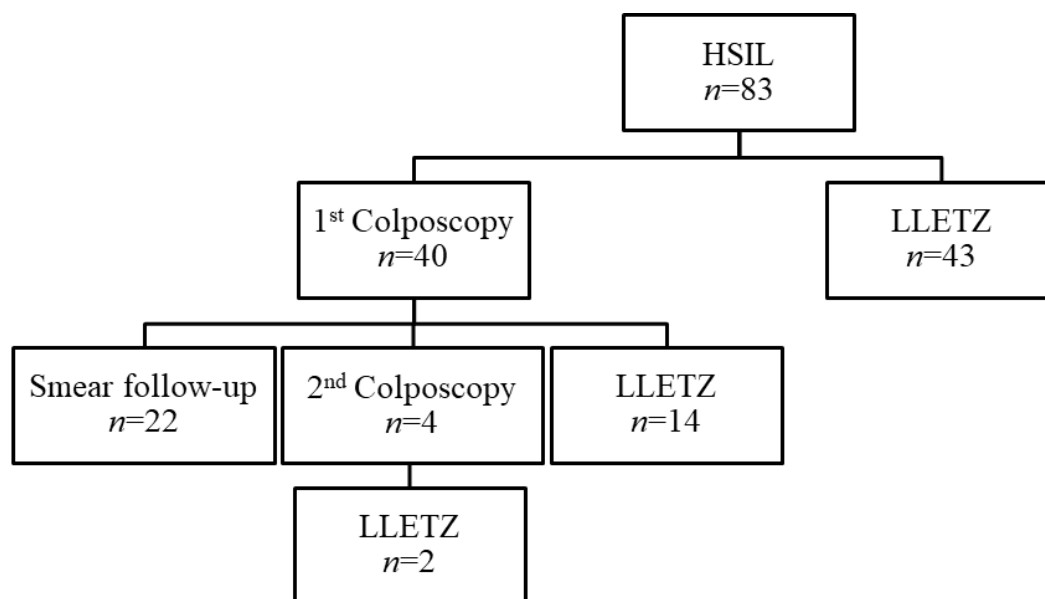
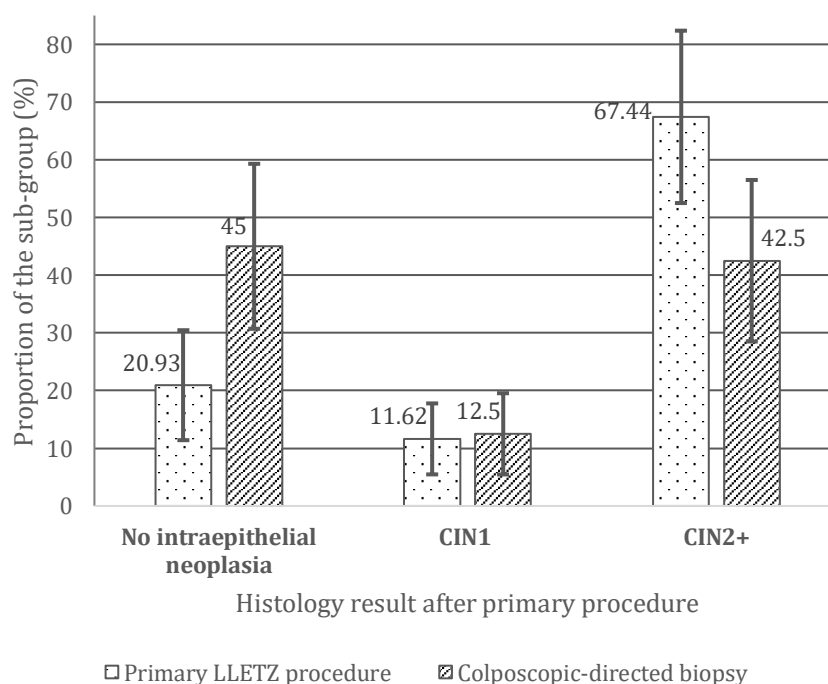


Table 1: Prevalence of HPV infection and HPV 16/18 serotype infection in the two sub-groups

	See-and-treat Approach % (95% CI)	Conventional Approach % (95% CI)
HPV Positivity	76.7 (61.4 - 88.2)	80.0 (64.4 – 90.9)
HPV 16 or 18	55.8 (39.9 – 70.9)	55.0 (38.5 – 70.7)

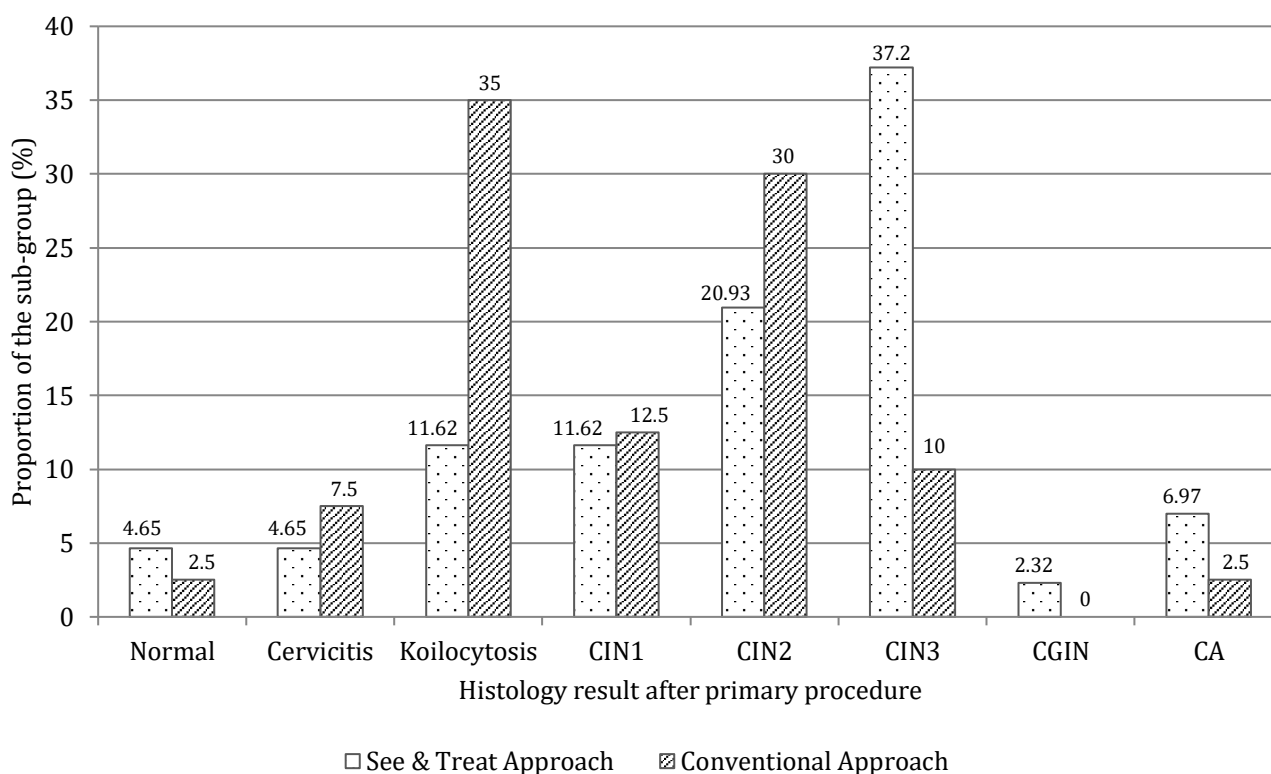
Figure 2: Histological outcome of the primary procedure performed in the two sub-groups



**Table 2: Primary histological outcome in two study sub-groups**

Histology	See & Treat Approach	Conventional Approach
	% (95%CI)	% (95%CI)
Normal/Cervicitis/Koilocytosis	20.9 (11.40-30.46)	45.0 (30.70-59.30)
CIN1	11.6 (5.47-17.77)	12.5 (5.46-19.54)
CIN2+	67.4 (52.50-82.38)	42.5 (28.50-56.50)

**Figure 3: Detailed breakdown of the histological outcome in the two study sub-groups**



**Discussion**

Papanicolaou’s discovery in the 1940s laid the foundation of cervical screening. The aim of cervical screening is to identify precancerous lesions at an early stage and thus reduce the incidence, morbidity and mortality from cervical cancer. Since the implementation of the UK NHS Cervical Screening Programme in 1988, the incidence of cervical cancer in the UK has decreased from 15 per 100,000 in 1986 to 8.9 per 100,000 in 2012 saving up to 4,500 lives per year.<sup>8</sup>

HSIL cytology results identify women at substantial risk of CIN2+. Each year approximately 1-2% of screened women are diagnosed with

CIN2+, which is found in some 60% of women with HSIL.<sup>3</sup> This compares well with an overall rate of 55.42% of CIN2+ diagnosed in our HSIL patient cohort, regardless of the management strategy.

In this local study a relatively higher incidence of CIN2+ pathology was identified in patients who underwent a primary excisional procedure as opposed to those who had a colposcopic-directed biopsy (67% and 42.5% respectively). Since the mean age, HPV prevalence and HPV 16 and 18 prevalence have been shown to be relatively equal in both sub-groups, one would expect the histological outcomes to be equivalent. Since LLETZ is a larger biopsy it enables better

histopathological representation of the cervical epithelial abnormalities and thus can be considered a gold standard in terms of histopathological diagnosis sensitivity.<sup>5</sup>

The see-and-treat approach is controversial due to the possibility of overtreatment. Thus, patients might be unnecessarily exposed to risks associated with a LLETZ procedure. These include infections, bleeding and preterm labour. The overtreatment rate following LLETZ in this study was 20.9%. This is referring to those patients with a normal, cervicitis or koilocytosis primary histological result. If LLETZ for CIN1 is also regarded as overtreatment, this figure increases to 32.5%. The overtreatment rate varies widely in different studies, but has been reported to be between 13.3-83.3% for LLETZ performed following HSIL cytology. The large majority of these studies do include CIN1 histologies when defining overtreatment, since CIN1 has a relatively high spontaneous regression rate.<sup>7</sup>

Excisional procedures carry a higher rate of complications than biopsies, both short-term and long-term. Short-term complications, though usually minor, include bleeding, pelvic pain, and infection. There is also conflicting evidence associating LLETZ procedures with a higher risk of preterm delivery in future pregnancies. Nonetheless, the see-and-treat strategy is the primary mode of treatment in several centres due to lower costs, decreased patient anxiety, and increased compliance making it appealing for patients at risk of being lost to follow-up.<sup>9, 10</sup> Nevertheless there has never been a local study assessing compliance to treatment and outpatient clinical follow-up. This would be of value, since the issue of non-compliance may not play a significant role in a small country with one state hospital.

Histological diagnosis from definitive treatment, such as excisional procedures, as already discussed, sometimes identify a more advanced stage of CIN than do colposcopic biopsies, where the severity of the cervical lesion may be underestimated.<sup>11</sup> Although cervical biopsies should represent the worst epithelial changes present on the cervix, this is not always the case in view of the subjective nature of colposcopic examination and possibly suboptimal colposcopic technique.

In a prospective study by Buxton EJ et al of 243 women, there was a higher rate of detection of severe lesions obtained following excisional

procedures versus colposcopically-directed biopsies; a difference of 25.5%.<sup>12</sup> Similarly in this study, a 24.9% discrepancy in CIN2+ detection was noted between the conventional approach and the see-and-treat approach, with the highest pick up rate obtained with primary excisional procedures. This potentially represents an underestimation of CIN, which can have potentially serious implications on patient outcome since it could lead to false reassurance for both clinician and patient.

Moreover, inter-observer variation in interpretation of colposcopic images exists, resulting in unfavourable colposcopic biopsies. There is also significant potential error due to the subjective nature of the examination as reflected in selection of the site for biopsy. In a prospective study by Pretorius RG et al in 2004, a comparison was made between histological results obtained from colposcopically-directed biopsies versus cervical biopsies taken at random without the guide of a colposcope. It was reported that 57.1% of colposcopy-directed biopsies were CIN2+ while only 37.4% of random biopsies showed this same histology result.<sup>13</sup> This implies that colposcopic skill has a significant effect on diagnosis and patient management. CIN2+ rates in our local study fall just above the rate of random biopsies described in the latter study. One could thus hypothesise that local colposcopic expertise could be limiting the accurate diagnosis of CIN2+ in HSIL patients.

With the mean age of the two patient cohorts being relatively equal, differences in outcome variables could be more reliably linked to respective mode of management. One would expect a discrepancy in the mean ages as women below the age of 24 years are advised to undergo a colposcopy first, while for women over 24 years a colposcopy or a primary excisional procedure may be considered. This is due to the higher rates of regression in women under 24 years of age and risks of preterm labour following surgical cervical trauma.<sup>12</sup> This could be due to a large proportion of older patients being channelled through the more conservative interval approach despite their age.

## Conclusion

Local management of patients with HSIL cytology remains controversial. Our results have shown that the conventional approach within our local setting potentially has inferior sensitivity in picking up CIN2+ lesions when compared to the

see-and-treat approach, with a discrepancy of 24.9%. This possibly represents a proportion of false negative results which could carry implications on patient outcome. On the other hand, primary excisional procedures were associated with an overtreatment rate of at least 20.9%, potentially subjecting patients to unnecessary risks.

Certainly, our local colposcopic service would benefit from improved colposcopic expertise, with the aim of improving the sensitivity of colposcopic-directed biopsies. Furthermore, the basis of the see-and-treat approach involves primarily assessing the cervix macroscopically via colposcopy, and only proceeding to a LLETZ if the colposcopic impression is suggestive of high-grade findings. Thus by improving the skill and confidence of the colposcopist, patients with HSIL who are found to have a macroscopically healthy cervix could be shifted to the three-step approach. In this way, the rate of overtreatment would be expected to decrease.

In conclusion, we recommend improving local colposcopic skill in order to reduce the rate of overtreatment and missed lesions at biopsy. This could be achieved by having these procedures performed by experienced and accredited colposcopists, as well as by setting up a structured colposcopy training programme for specialty trainees. This study could be repeated in the future once the necessary improvements to our colposcopic service have been enacted.

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